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Review Article

A Review on Therapeutic Management of Chronic Hepatitis B Infection

Abstract

The current therapeutic goal in the management of chronic hepatitis B (CHB) infection is to persistently suppress hepatitis B virus (HBV) replication and prevent its progression to liver failure and the development of hepatocellular carcinoma (HCC). At present, the therapeutic strategies for CHB includes either a short course of pegylated-interferon-alfa (PEG-IFNα) and/or a long term course of nucleos(t)ide analogues (NA's). NA's are more preferable to PEG-IFNα, majorly for its easier route of administration and excellent tolerance and safety profiles. Entecavir (ETV) and tenofovir (TDF) are the current first line options for its potency to maintain sustained virological response (SVR) in almost 100% of the adherent individuals along with minimal to no long-term resistance. These sustained inhibitions of HBV replication have been shown to be associated with histological improvement, modifying the long-term outcomes. However, HBsAg seroconversion, the best surrogate marker for viral clearance is still unachievable with the current first line agents and hence the risk for hepatocellular carcinoma (HCC) still exists among them. This makes us to still consider, a finite duration of PEG-IFNα that has shown considerable results with regards to HBsAg loss, as an attractive add-on or monotherapy option despite its adverse events profile. Existing evidences do not recommends its usage. However, numerous studies are ongoing and also further studies to evaluate the reliable baseline predictors of response to PEG-IFNα and early on-treatment stopping rules based on age, alanine aminotransferase levels (ALT), HBV DNA levels and HBsAg kinetics would be ideal.

Abbreviations

CHB: Chronic Hepatitis B; PEG-IFNα: Pegylated Interferon-alfa; NA's: Nucleos(t)ide Analogues; ETV: Entecavir; TDF: Tenofovir; HCC: Hepatocellular Carcinoma; SVR: Sustained Virological Response; ALT: Alanine Aminotransferase;

Introduction

Chronic hepatitis B (CHB) infection is defined at large by the presence of hepatitis B surface antigen (HBsAg) for more than 6 months; though some patients may test positive only for anti-HBc without HBsAg or anti-HBs [1]. An estimated 240 million people are chronically infected with hepatitis B and a 15% to 40% lifetime risk of death exist in these affected population due to serious sequelae such as cirrhosis, hepatic decompensating, and hepatocellular carcinoma (HCC) [1,2]. The increasing prevalence, morbidity and mortality of CHB can be linked to its diverse and variable natural course; which in general, is serologically illustrated either by the presence or absence of hepatitis B virus (HBV) e antigen (HBeAg) indicating earlier and late phases of the disease, respectively [3,4]. The ultimate goal of CHB therapy is to arrest the progression of liver injury and to prevent the development of liver failure, HCC and hence liver transplantation. Despite the advent of potent anti-HBV agents such as interferon-alpha (INFα) and nucleos(t)ide analogues (NA's), the current management is majorly ineffective in eradicating the virus, providing only apparent virological suppression [3,5]. Hence an absolute cure or functional cure, where the risk of death from liver disease is same as a person who was never infected or same as a person with naturally resolved infection, remains impracticable yet [5]. Also, though the existing practice guidelines such as that of American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), and Asian Pacific Association for the Study of the Liver (APASL) assist physicians in the diagnosis and optimal management of CHB; they are still expected to individualize the management considering various factors like cost-effectiveness, compliance, efficacy and duration of anti-viral agents, existence of co-infections etc. [1,3,4]. This article reviews the basis for those guideline recommendations, the natural history of the disease, treatment options and what we do in our practice to illustrate factors that may influence the management of CHB.

Natural history of chronic hepatitis B infection

Continuous advances have been made in understanding the natural history of the disease, which is majorly determined by the interplay between host-immune responses and viral replication. Such knowledge and identification of which natural history phase of the disease the patients are in would be the ideal first step in the management of CHB infection, as the criteria and endpoints of treatment differ accordingly. The dynamic natural course of CHB infection can be categorized into at least five phases; however, these need not be in sequence and exist in all patients with the disease [6].

- The initial phase is characterized by high levels of HBV replication with no evidence of active liver disease and hence termed as "*high replicative, low inflammatory phase*". This phase is more common in patients with prenatally acquired CHB infection and is widely known as the "*immune tolerant phase*", for the inability of immature immune system to

identify the virus aided by the HBeAg protein [1,3]. However, researchers state a hypothesis of trained immunity, evidenced by enhanced innate immune cell maturation and Th1 development resulting in a similar T cell response to that seen in the immune clearance phase of CHB [7,8]. These immune trained HBeAg positive patients are characterized by very high levels of serum HBV DNA that is commonly above 20,000 IU/mL or 1 million IU/mL, normal to low levels of serum aminotransferases, and no to minimal liver necroinflammation and fibrosis [1,3]. During this phase, the reverse transcriptase properties of HBV may support its integration randomly into the host hepatocyte DNA resulting in persistently elevated HBV DNA levels over many years; thereby increasing the risk of cirrhosis and HCC.

- In the "*immune clearance phase*", the host's immune system initiate it's response to HBV resulting in hepatocyte injury. It is more common and rapidly reached in patients infected during adulthood resulting in spontaneous HBeAg clearance, paralleling the maturity of innate and adaptive immune responses. Patients early in this phase are mostly HBeAg positive, with high levels of serum HBV DNA, elevated levels of serum aminotransferases, and moderate to severe liver necro-inflammation with more progression to fibrosis [1,3]. Over the time, in many cases spontaneous HBeAg clearance occurs, accompanied with exacerbations in serum alanine aminotransferases (ALT) and HBV DNA levels [9]. This phase ends with the appearance of anti-Hbe and such clearance either spontaneously or by antivirals during early stages of the disease has been shown to significantly reduce the risk of complications [3].

- Patients in the "*HBeAg-negative CHB phase*" have HBV virions in the precore and/or the basal core promoter regions with nucleotide substitutions. These patients are generally characterized by HBeAg negativity, with periodic reactivation due to ineffective immune clearance, resulting in moderate to high levels of viral load (usually >2000 IU/ml) and aminotransferases levels [1,3]. The serum HBV DNA and ALT levels are much lower compared to HBeAg positive individuals in the immune clearance phase. They have continued necro-inflammation in the liver and are at risk of complications due to low rates of prolonged remissions.

- Predominantly patients in the "*non-replicative phase*"; widely known as "*inactive HBV carrier*" phase, are characterized by seroconversion of HBeAg to anti-Hbe, very low or undetectable serum HBV DNA levels (usually <2000 IU/ml) and normal serum aminotransferases (approximately 40 IU/m) conferring a favorable long-term outcome due to immunological control of the infection [3,6]. However, care should be taken in categorizing these patients as inactive carriers with minimum three consecutive serological readings over a 12-month period of observation.

- Patients in the "*occult HBV phase*" are defined by the loss of the hepatitis B surface antigen, hence also termed as "*HBsAg-negative phase*". However, a low level of HBV replication persist in the liver, characterized by intrahepatic presence of cccDNA chromatinized episomes. Most patients in this phase have very low to undetectable HBV DNA levels, with anti-HBc and with or without anti-HBs. Generally they have a better prognosis, if HBsAg loss occurs before the onset of cirrhosis [3,6].

Factors related to chronic hepatitis B progression

The clinical scenario following hepatitis B infection is determined by the interplay of other associated factors such as sex, age, genotypes, co-infections, alcohol consumption etc. Hence its consideration should always be taken prior to the initiation of therapy for CHB.

Genotype: To date, 10 genotypes (A through J) have been reported across different geographic regions and numerous studies have revealed their clinical importance on the chronicity of the disease, response to therapy and progression to complications. Genotype C, which is common in Asian population, have been shown to be associated with the longest average age of HBeAg seroconversion; thereby carrying the highest risk for HCC than any other genotypes [10]. Genotype B is regularly divided into Bj (B1 and B6, found in japan) and Ba (B2-5, found in rest of Asia) sub-types. The genome of Ba group has a portion of genotype C genome; thereby making these people prone for complications and basal core promoter (BCP) mutations than those with Bj [11]. Persons infected with genotype D, which is common in Eastern Europe, Southern Europe and Middle East; have been shown to go frequently into either "HBeAg-negative CHB phase", harboring precores variants with high risk for HCC or into "inactive HBV carrier" with low risk for complications [12,13]. Genotype A, which is classified into A1 and A2, is widespread in Western Africa, sub-Saharan Africa and Northern Europe. Genotype A1 is associated with HCC in HBeAg negative young patients with low HBV DNA levels and cirrhosis rate [13]. Though, genotype A2 is associated with HCC in older persons, its risk is comparatively lower to genotype D with higher clearance of HBsAg [14]. Across different genotypes, though treatment response to nucleos(t)ide analogues have been reported to be similar, genotypes A and B have shown better response rates to interferon substitutes than genotypes C, D [15,16]. The recently included genotypes are genotype I and J, reported in Vietnam, Laos and in Ryukyu islands of Japan, respectively [17,18]. However, its clinical importance is not yet clearly studied.

Age: Persons who are infected via perinatal transmission from HBeAg-positive mothers tends to be in the "*high replicative, low inflammatory phase*" phase of the disease for a longer duration. These young infected individuals are associated with lower rate of clearance of HBeAg and poor prognosis, compared to the older individuals [19].

Co-infections: Patients with chronic hepatitis B may be co-infected with more than one genotype or with other viruses. Though studies have demonstrated co-infections with different HBV genotypes, it's clinical consequences still remains unclear [20]. Coexistent hepatitis C virus (HCV) infection is mostly either acute co-infection of HCV and HBV, or acute HCV on preexisting chronic HBV; where HCV becomes the dominant virus and suppresses HBV DNA levels. However, both these presentations have been reported

to increase the risk of severe hepatitis, fulminant hepatic failure, cirrhosis and HCC development compared to patients infected by either virus alone [21]. Hepatitis delta virus (HDV) is an incomplete RNA virus that obliges the presence of HBV within the hepatocytes to complete its assembly and replication. Such interactions either presents as a co-infection with HBV or as super-infection occurring in chronic HBV carriers. However, on contrary to HCV co-infection with HBV, HDV co-infection is usually transient and self-limited, with rates of chronicity and complications similar to HBV mono-infected patients [22]. Super-infection with HDV, in most cases presents as self-limiting severe acute hepatitis with establishment of HDV chronicity and exacerbation of the pre-existing HBV chronicity [23]. Co-infection of HBV with HIV is a rising global health problem with lower rates of spontaneous HBeAg seroconversion, and hence the serious sequelae. Also, these patients may have occult HBV infections characterized by the presence of anti-HBc, high HBV DNA levels, without HBsAg [24].

NASH/NAFLD: Non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) is an important cause of chronic liver disease, with increasing prevalence paralleling to the global rise of obesity, insulin resistance, and type 2 diabetes mellitus (T2DM). Studies analyzing NAFLD or NASH in chronic hepatitis B patients have shown its added impact on the development of fibrosis [25].

Cirrhosis: Several studies have shown the strong associations between HBeAg and high levels of HBV DNA to the development of cirrhosis. Also, though cirrhosis is an independent risk factor for HCC, its absence doesn't rule out the development of the HCC in CHB patients [26].

Mutations: Several prospective studies have established that, BCP mutation [adenine (A) to thymine (T) transversion at nucleotide 1762 together with a guanine (G) to adenine (A) transition at nucleotide 1764] and precore mutation [nucleotide 1896 mutation from guanine (G) to adenine (A)] are independent risk factors for HCC in CHB patients even after adjusting for their genotypes. On the other hand, the presence of the PC mutation was associated with a lower risk of developing HCC [27].

Available treatment options

The U.S. Food and Drug Administration (FDA) have approved seven agents for the treatment of CHB [28]. The first licensed agent for the treatment of chronic HBV infection was the conventional form of interferon alfa (in 1991); which have antiviral, antiproliferative, and immunomodulatory effects. Pegylated interferon (PEG-IFNα), an agent that is almost identical to that of standard IFNα, was licensed in 2005. Other agents that are currently in use are nucleoside and nucleotide analogues; which are pure anti-virals that act via suppression of HBV replication through inhibition of the reverse transcriptase and DNA polymerase activities. Lamivudine, a nucleoside analogue, was the first among them to be licensed in 1998. During the past decade, two other nucleoside analogues; entecavir (in 2005) & telbivudine (in 2006), and two nucleotide analogues; adefovir (in 2002) and tenofovir disoproxil fumarate (in 2008) were licensed.

The ultimate goal of CHB treatment is to prevent or decrease the development of cirrhosis, hepatic failure and HCC. These endpoints are reached by the suppression of viral replication, which are monitored through parameters such as reduction in HBV DNA to undetectable levels; reduction of serum ALT to normal levels; loss of HBeAg with or without detection of anti-HBe; and improvement in the histological findings. But, viral eradication is nearly unachievable because of the tendency HBV to integrate into the host genome or remain latent as cccDNA [29]. Considering the extensive cost, the risk of adverse events and the drug resistance with long-term treatment, the most important question that arises is, which CHB patients need to be treated now and which patients can be monitored and have treatment deferred. And, as the efficacy and the optimal timing to initiate antiviral strategies are greatly influenced by the dynamic course of the disease and the above-mentioned host, viral, and environmental factors associated with progression of CHB; we have tried to focus on the current therapeutic strategies on two separate grounds based on the HBeAg status.

Optimal management for HBeAg positive chronic hepatitis B patients

Approach to HBeAg positive patients for anti-viral therapy (Figure 1):

a) During the high proliferative, low inflammatory phase: As mentioned earlier, these patients usually have persistently normal ALT levels (PNALT) and very high HBV DNA levels without any evidence of liver disease. Studies have also shown low rates of anti-HBe seroconversion in patients who were treated during this phase of the disease [30]. Hence treatment can be deferred in most scenarios. However, the severity of histological lesions varies widely across studies in HBeAg positive patients with PNALT [31]. In these patients, the continued high HBV replication and a prolonged HBeAg positive phase can increase the risk of HCC and the progression of liver disease. Hence, it is wise to perform liver biopsy and treat the patients with PNALT after careful consideration of the associated host factors [1,3]

- Treatment can be deferred in young patients < 30 years without any evidence of liver disease and without family history of HCC or cirrhosis. Follow-up every 3-6 months with serum ALT levels and serum HBV DNA levels and every 6-12 months with HBeAg are advisory.
- Biopsy is recommended in patients > 30 years with or without family history of HCC or cirrhosis to make therapeutic decisions.
- A positive family history of HCC should however reduce the age limit for any therapeutic decisions.

b) During immune clearance phase: The judgment for initiating treatment in patients during the immune active phase depends majorly on the baseline serum ALT and HBV DNA levels.

- Current guidelines recommend treatment commencement in all patients with baseline ALT > 2 ULN (upper limit of normal) and HBV DNA > 20 000 IU/ml, even without the need of biopsy as moderate-severe necroinflammation and significant fibrosis is universally seen in these patients [1,3].

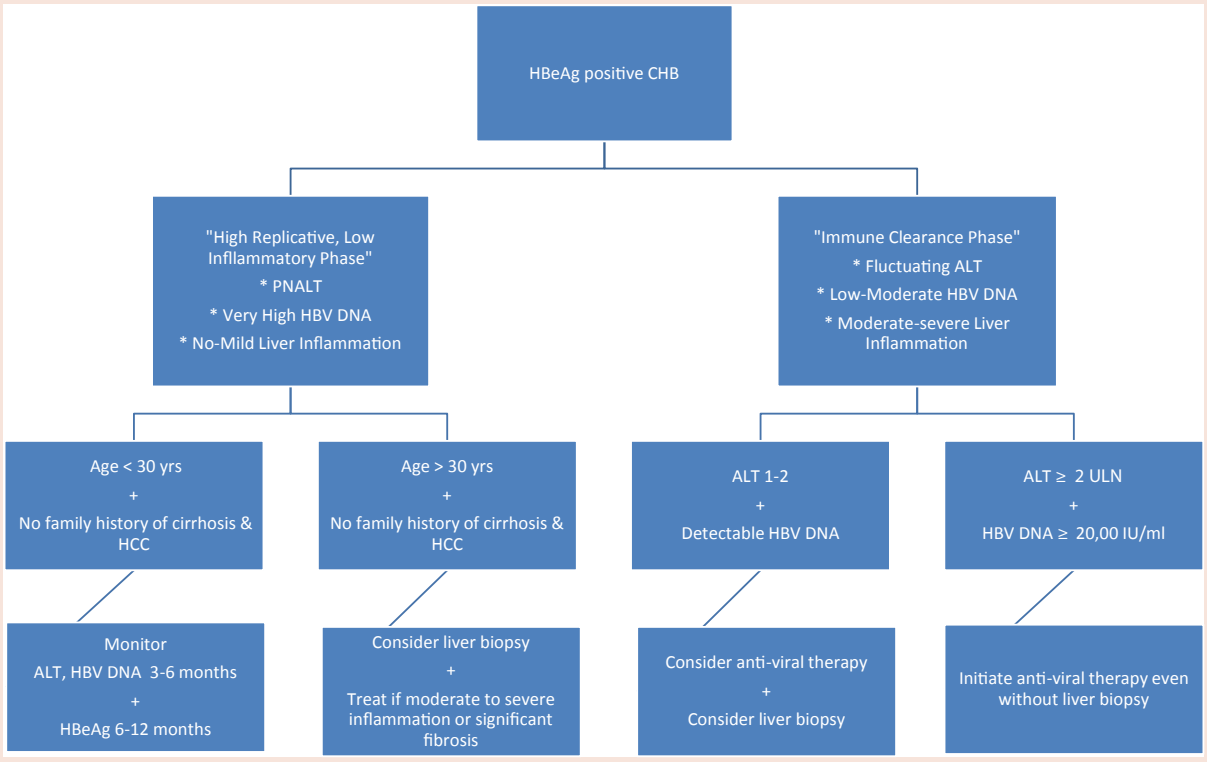

Figure 1: Approach to HBeAg Positive Chronic Hepatitis B patients.
CHB: Chronic hepatitis B; ALT: Alanine aminotransferase; PNALT: Persistently normal ALT; ULN: Upper limit of normal; HCC: Hepatocellular carcinoma.

- In patients with ALT between 1–2 ULN, EASL recommend treatment consideration and liver biopsy to assess the severity of liver disease [3]. However, a close follow-up of ALT and HBV DNA levels every 3-6 months for treatment consideration is also being practiced in such patients.
- Age > 40 years or an increasing or stable HBV DNA for 6 months on follow-up, is a strong recommendation to have a liver biopsy and be started on treatment if there is evidence of moderate-severe necroinflammation and/or significant fibrosis [1]. With decreasing HBV DNA on follow-up regardless of ALT values, these patients can be followed up closely without treatment and wait for spontaneous anti-HBe seroconversion [31].

c) Cirrhotic state: Treatment is generally initiated in all HBeAg positive CHB patients with compensated cirrhosis and detectable HBV DNA, even if ALT levels are normal. With any event of decompensation, urgent start of anti-viral therapy is recommended in all patients irrespective of HBV DNA levels and ALT levels [1,3,4].

Role of interferon's in HBeAg (+) CHB patients' management:

a) Standard vs. pegylated IFN: Standard IFNα, which was first drug available for the treatment of HBeAg (+) CHB infection, has now been largely replaced by pegylated (PEG)-IFNα. This clinical scenario is chiefly attributed to PEG-IFNα's pharmacokinetic profile of longer half-life, stable serum concentrations and once a week 180 mcg subcutaneous administrations for 48 weeks, compared to thrice weekly injections of standard INF [32]. Also, studies have stated a greater combined sustained viral response (SVR) rate, defined as combination of HBeAg loss; HBV DNA suppression; and ALT normalization, following a 24-week course of PEG-IFNα-2a compared to standard IFNα-2a [33].

b) End points for Treatment: Though the ideal end point of therapy is HBsAg loss, with or even without seroconversion to anti-HBs, studies have indicated a low rate of HBsAg seroconversion of 3–5% in HBeAg (+) patients after 6 months of therapy [34,35]. Hence, a more convincing approach would be at targeting a sustained or maintained virological remission (defined as loss of HBeAg); virological response (defined as an HBV DNA concentration of less than 2000 IU/ml); and biochemical response (defined as normalization of ALT levels).

c) Predictors of response to treatment: Multi-variable analyses of HBeAg positive CHB patients treated with PEG-IFNα in large international studies have shown that low HBV DNA (<2 x 10^8 IU/ml), high ALT (>2-5 ULN), and high activity scores on liver biopsy (≥ A2) are baseline predictors to anti-HBe seroconversion [36]. Also, HBV genotype A with either high ALT or low HBV DNA levels, HBV genotype B & C with both high ALT and low HBV DNA levels had a high probability of achieving an SVR at 6months post-treatment [37,38].

HBsAg: The latest handiness of commercial assays for HBsAg quantification has aided studies to investigate the role of HBsAg levels as a predictor of response to PEG-IFNα. In HBeAg positive CHB patients, not baseline HBsAg levels, but on-treatment HBsAg levels were shown to be a useful predictor of response to PEG-IFNα. Large multicenter trials done in Asian patients with HBeAg positive CHB, have displayed a high probability of 55% and 45% of anti-HBe seroconversion at 6 months post-treatment in subjects who achieved HBsAg levels <1500 IU/ml at 12 weeks of PEG-IFNα therapy [39,40]. In the same cohort, the cumulative rate of anti-HBe seroconversion at 6 months post-treatment was found to be 0% and 15% in subjects who achieved HBsAg levels >20,000 IU/ml at 12 weeks of PEG-IFNα therapy. Recently, long-term follow-up studies analyzing the PEG-IFNα prediction rules based on HBsAg levels in HBeAg positive CHB patients, have demonstrated a negative predictive value (NPV) of 92-98% for 12-week stopping rule based on HBsAg >20,000 IU/ml for no response in patients with HBV genotype B or C; NPV of 97-100% for 12-week stopping rule based on absence of any decline in HBsAg for no response in patients with HBV genotype A or D; and NPV of nearly 100% for 24-week stopping rule based on HBsAg >20 000 IU/ml for no response in patients irrespective of their genotype status [40,41].

Anti-Hbc: The use of quantitative baseline anti-Hbc as a predicator of response to PEG-INFα has been studied recently. In HBeAg positive cohort treated with PEG-INFα, results have shown an HBeAg seroconversion rate of 65.8% in patients with baseline anti-Hbc ≥ 4.4 log 10 IU/ml and baseline HBV DNA < 9 log 10 copies/ml, compared to 25.4% in patients with other baseline characteristics [42]. However in the same cohort, the on-treatment HBsAg levels of <1500 IU/ml at 24 weeks of PEG-IFNα therapy, failed to show a predictor response to HBeAg seroconversion, which is in contrary to the results seen in previous studies. Another study in HBeAg positive patients, have shown that baseline anti-Hbc can be considered as an independent predictor of response to PEG-INFα therapy. Results showed that, increasing order of the baseline anti-Hbc (<5,000 IU/ml to ≥ 50,000 IU/ml) was positively correlated with rates of HBeAg seroconversion (7.7% to 52.6%), virological response rates (7.7% to 47.4%) and combined response rates (7.7% to 42.1%) [43]. However, further investigations are required to validate these results.

HBeAg: Despite the lack of standard commercial HBeAg assays, studies have also tried to investigate the role of HBeAg levels as a predictor of response to PEG-IFN. Data from a large phase III trial in patients with HBeAg positive CHB treated with PEG-IFNα-2a, exhibited a probability rate of > 50% of anti-HBe seroconversion at 6 months post-treatment in subjects who achieved HBeAg level <10 PEIU/ml at 24 weeks of therapy [44]. In the same study, the cumulative rate of anti-HBe seroconversion at 6 months post-treatment was only 4% in subjects who achieved HBeAg ≥100 PEIU/ml at 24 weeks of therapy. However, a more recent study has suggested the role of HBeAg levels as a predictor of response to PEG-IFNα, is influenced by the presence of precore and basic core promoter mutants and hence should not be routinely used for monitoring of PEG-IFNα therapy [45].

However, the application and utility of quantitative measures of HBsAg and HBeAg are being extensively researched in the field of HBV therapeutics that might provide new dimensions for predictors of response.

d) Efficacy and durability of therapy: Data from large international trials have shown better rates of HBeAg seroconversion in the order of approximately 30%; at 6 months following 12 months of PEG-IFN, compared to those with shorter duration or with inferior dosage [34,35]. However the rates of HBsAg loss and HBV DNA suppression to <400 copies/ml following 12 months of treatment were only around 3-5% and 7-14%, respectively.

Durability after anti-HBe seroconversion following PEG-IFNα was very satisfactory with studies showing 83% of initial responders maintained the serological response at 12 months post-therapy, among which 69% maintained serum HBV DNA <10 000 copies/ml and 38% maintained serum HBV DNA <400 copies/ml [46]. Also HBsAg negativity was maintained in 30% of initial responders, after a mean follow-up of 3 years [47].

Role of nucleos(t)ide analogues in HBeAg positive CHB patients management:

a) Early vs. late NA's: The advent of nucleos(t)ide analogues (NA's) have revolutionized the management of CHB infection worldwide; chiefly attributed to its oral administration, potent anti-viral activity and lesser side effects. A major drawback of earlier NA's such as lamivudine (3TC) and adefovir was the high rate of antiviral drug resistance. Lamivudine is associated with the highest rate of resistance, increasing with duration of treatment from 14% - 32% after 1 year of treatment to as high as 60% - 70% after 5 years of continuous therapy [48,49]. Primarily, the mutation associated with its resistance involves substitution of methionine in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the HBV DNA polymerase for valine or isoleucine (rtM204V/I, rtV173L) and substitution of methionine by a leucine in an upstream region (rtL180M) [50]. Despite the initial low resistance rate with adefovir, the cumulative resistance rate in a phase III clinical trial in HBeAg-positive patients was estimated to be 20% after 5 years of continuous therapy [51]. Primary mutations associated with adefovir resistance have been described to be through substitution of threonine by asparagine N236T and valine or threonine substitution by alanine (A181V/T) [52]. In case of telbivudine, though the rate of resistance is lower than 3TC; results from clinical trials have shown that the resistance rate is substantial and increases exponentially after the first year of treatment from 5% to 25% at the end of second year itself [53]. To date, only M204I has been observed to be the primary mutation associated with telbivudine resistance [54]. However, the new NA's such as entecavir (ETV) and tenofovir (TDF) have high barriers to resistance. Preliminary data from the studies in NA naïve HBeAg-positive patients, suggest that the rate of entecavir resistance was observed only to be 3.6% by week 96 and 1.2% % after 5 years of treatment [55,56]. This resistance to entecavir appears to occur through a two-hit mechanism with initial selection of M204V/I mutation followed by amino acid substitutions at rtT184, rtS202, or rtM250 [57]. Recently, the rate of TDF resistance was reported to be 0% after 5 years of treatment, in phase 3 trials of NA-naive patients [58].

Apart from the resistance scenario, ETV and TDF were shown

to be the most potent drugs of all the NA's for suppressing HBV replications in patients with HBeAg positive CHB infection. A phase III randomized clinical trial studying ETV and 3TC in patients with compensated liver disease, showed that entecavir resulted in significantly higher rates of undetectable or <60–80 IU/ml serum HBV DNA levels (67% vs. 37%), normalization of ALT levels (68% vs. 60%), and reduction in necroinflammatory activity (72% vs. 62%), after 48 weeks of treatment [59]. However, the rates of anti-HBe seroconversion were similar between the groups (21% vs. 18%). In a similar study comparing tenofovir and adefovir response after 48 weeks, the cohort on tenofovir had better rates of undetectable or <60–80 IU/ml serum HBV DNA levels (76% vs. 13%), normalization of ALT levels (68% vs. 54%), with similar rates of histological response (74% vs. 68%) and HBeAg seroconversion (21% vs 18%) [60]. though limited and inconclusive, data have shown better efficacy rates of ETV and TDF in lamivudine and adefovir resistant HBV infection [61,62]. Current scientific guidelines recommend oral administration of entecavir of dose 0.5 mg daily in treatment naïve patients and 1 mg daily in lamivudine-refractory/resistant patients. The approved dose of tenofovir is 300 mg orally once daily. Both agents' doses should be adjusted for patients with estimated creatinine clearance 50 mL/min [1,3]. Adefovir, though have demonstrated maximum nephrotoxic potential, its consideration for treatment of CHB with lower doses have shown better HBeAg seroconversion rates, HBV DNA suppression, ALT normalization, durability of response and long term outcomes [51,63].

b) Endpoints for treatment: In HBeAg-positive patients treated with NA's, though seroconversion to anti-HBe is a desired intermediate endpoint to stop the treatment, these patients can continue therapy until they achieve HBsAg loss. This end-point is considered to be ideal, as it has been associated with complete and permanent remission of CHB activity and excellent long-term outcomes.

c) Predictors of response to treatment: Preliminary data suggest that low viral load (HBV DNA $<10^8$ IU/ml), high serum ALT levels and high activity scores on liver biopsy are solid pretreatment predictors to anti-HBe seroconversion [60,64,65]. The results have been striking with the probability of HBeAg seroconversion differing greatly from <1% in HBeAg positive patients with normal ALT levels, to 30% to 40% in patients with ALT levels >5-fold the upper normal limit, treated with ETV, LAM or ADV [66].

HBsAg: Also, studies have tried to elucidate the role of decline in HBsAg during NA treatment in determining subsequent HBeAg or HBsAg loss. In a long-term TDF trial in HBeAg positive patients, HBsAg loss were associated with loss of HBeAg in the first 24 weeks of TDF treatment, high baseline HBsAg levels, an HBsAg slope from baseline to week 12 and an ALT flare in the first 12 weeks of therapy [67,68]. However, further studies are required to analyze the role of HBsAg kinetics during NAs therapy.

Anti-HBc: A recent study in a HBeAg positive cohort treated with telbivudine, showed a HBeAg seroconversion rate of 37.1% in patients with baseline anti-Hbc ≥ 4.4 log 10 IU/ml and baseline HBV DNA < 9 log 10 copies/ml, compared to 14.5% in patients with other baseline characteristics [42]. Also, combined with the on-treatment HBsAg levels of <1500 IU/ml at 24 weeks of NA therapy showed a predictor response of HBeAg seroconversion 48.6%. Though these predictors have shown positive results, further studies are required in validating its value in predicting the efficacy of NA's.

d) Efficacy and durability of therapy: Phase III clinical trial's outcome have exhibited that prolonged treatment with NA's are associated with increase in the rates of anti-HBe seroconversion. The cumulative rate of anti-HBe seroconversion ranges approximately from 20% in patients treated with ETV or TDF at 1 year to 40% at 7 years of TDF therapy [56,69].

However, the durability of anti-HBe seroconversion is questionable in patients treated with NA's, with rates ranging from 40% to 80% upon discontinuation of NA therapy [70,71]. This disease progression after HBeAg seroconversion was suggested in a study is due to the emergence of precore and core promoter mutations, which occurs even before HBeAg seroconversion [72]. An overall incidence of core promoter mutations has been reported to be as high as 88.1% in such patients. These evidences have strongly recommended the clinical practitioners to continue NAs for 12 more months after anti-HBe seroconversion, to have a long follow-up after stopping NA's and to maintain persistently low HBV DNA levels, which in specific could be used as predictor of disease progression to either HBeAg-negative CHB or HBeAg seroreversion. Evidences also support prolonged treatment with ETV or TDF increase the rate of HBV DNA levels of <60–80 IU/ml to almost 100% with continued maintenance over time [56,69]. Rates of HBsAg loss following 1 year of NA's treatment have been less noteworthy ranging from 0-1% among the less potent NA's such as adefovir, lamivudine, telbivudine to 3-5% among ETV and TDF [56,69]. However, the long-term TDF trial in HBeAg positive patients have shown promising results with respect to cumulative rate of HBsAg loss from 8% after 3 years of therapy to 12% after 7 years of therapy [73].

Recent studies involving ETV and TDV in patients with baseline cirrhosis have shown considerate positive impact in prevention of progression of fibrosis and regression of cirrhosis, after 5-6 years of therapy [74,75]. Recently, another large cohort study matched for the risk of HCC with historical controls, showed a reduction in the incidence of HCC with ETV, with higher response rates among patients with risk factors for HCC such as cirrhosis [76]. In a long-term study with TDV, incidence rates of HCC in patients with and without cirrhosis were reported to be 4.5% and 1.5% respectively. The salient features of this study are that, the HCC incidence rates in patients without cirrhosis were lower than that predicted by the REACH-B model and this is the first evidence to reveal a positive effect of HCC risk reduction in patients without cirrhosis on NA therapy, which contradicts results of the meta-analysis of 27 trails [77]. Also, earlier randomized controlled trials using lamivudine and adefovir have shown a similar response with clear reduction in complications [78,79].

Selection between PEG-IFNα vs. NA's in HBeAg positive CHB patients' management (Figure 2): The preference between the drug options available for the management of HBeAg positive CHB patients has to be considered from two viewpoints i.e. patient

preference and physician preference. Patients generally prefer oral treatment compared to injections; thus, giving NA's which are taken as one tablet per day, an important advantage over PEG-IFNα which are administered weekly as subcutaneous injections. Also several data from clinical trials have shown the excellent tolerance and safety profile of NA's over PEG-INFα, which is associated with several contraindications and a wide range of adverse events such as influenza-like illness, anorexia, weight loss, emotional liability etc. [35,80].

Between the ETV and TDF, which are the current first-line NA options, ETV appears to be safer as few studies have reported about the potential nephrotoxicity of long term TDF therapy [81]. However, the rates of decline in creatinine clearance or hypophosphataemia are very low (<1%) in CHB patients after 5 years of TDF therapy [75]. Also, it should be noted that except telbivudine, minimal declines in creatinine clearance have been reported with all NAs, requiring dosing adjustments when creatinine clearance is <50 ml [1,3].

From the physician viewpoint, NA's holds an advantage over PEG-IFNα as its wants less frequent on-treatment monitoring due to its superior safety profile and excellent tolerance levels [34]. Also NA's is applicable in patients at different stages of HBV infection such as chronic hepatitis B, patients with cirrhosis, decompensated patients and in the liver transplant setting with excellent results and easy follow-up. The only drawback of NA's over PEG-INFα is the indefinite time period of therapy, which might pose a threat to its safety profile, raising concerns about compliance and thereby its efficacy [82]. This scenario should be compared to that of the management of non-communicable diseases such as diabetes mellitus and hypertension, where patient education about adherence to therapy has changed the entire outlook of the disease management. At the same time, physicians should consider PEG-INFα as an attractive option with respect to sustained virological response with finite duration too.

Combination Therapies: Another theoretically attractive concept in managing patients with CHB infection, is the addition of HBV agents of different mechanism of action or the same action for improving the HBsAg clearance rates. In one randomized controlled study, addition of TDF to ETV in patients with very high baseline viral load of HBV DNA ≥108 IU/ml.\, showed a significantly higher viral suppression than ETV therapy alone (70% vs. 60%) [83]. Similar results were shown in another study comparing TDF vs. TDF + emitricitabine, however the rates of HBeAg and HBsAg clearance were the same [30].

With regards to the efficacy of NA's and PEF-INFα combination therapy in the management of HBeAg positive CHB patients, a recent

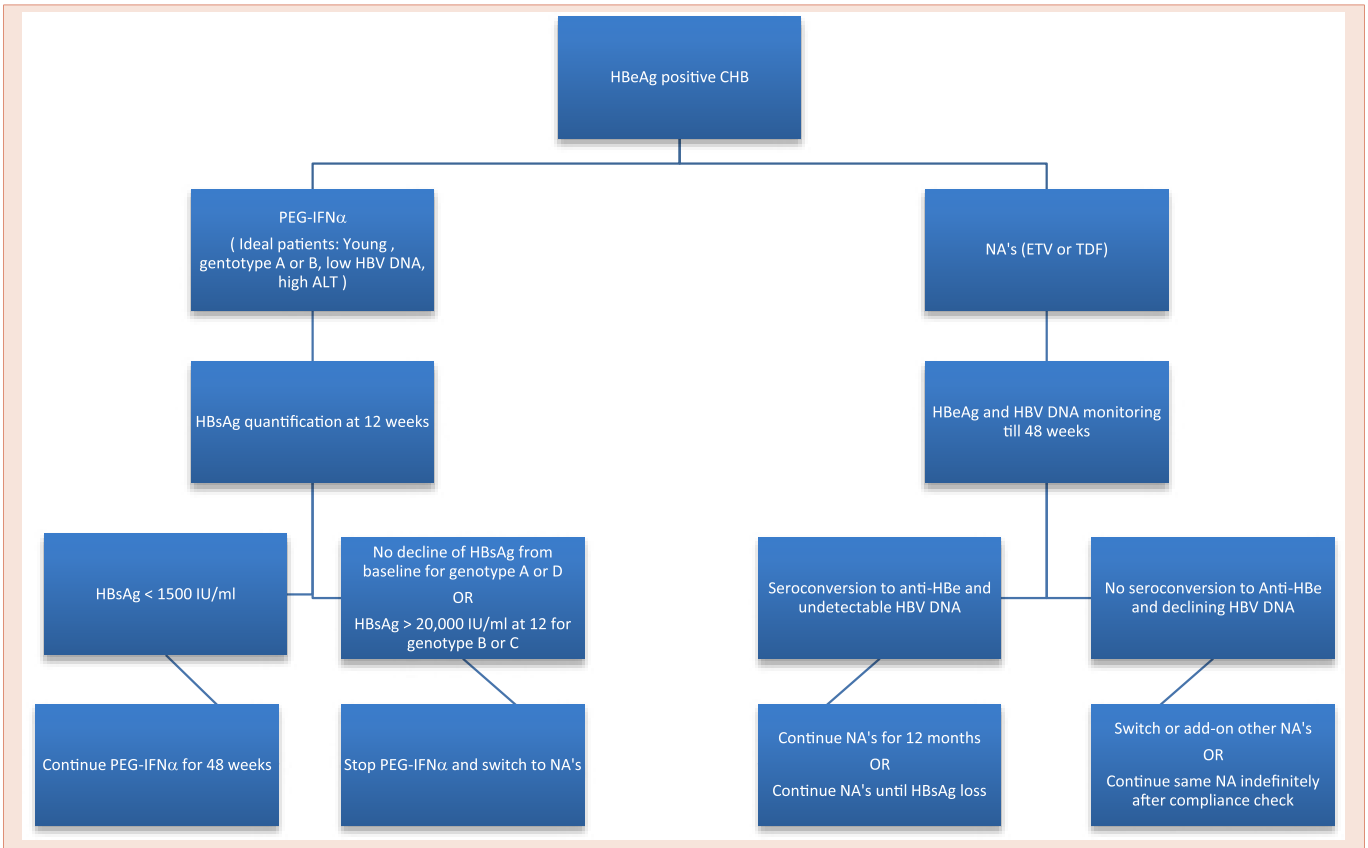

Figure 2: Anti-viral Therapy Options for HBeAg Positive Chronic Hepatitis B patients.
CHB: Chronic hepatitis B; PEG-INFα: Pegylated Interferon Alpha; NA's: Nucleos(t)ide analogues; ETV: Entecavir; TDF: Tenofovir; ALT: Alanine aminotransferase; HBsAg: Hepatitis B surface antigen.

meta-analysis have shown enhanced rates of undetectable HBV-DNA, HBeAg loss and HBsAg loss with no significant difference in ALT normalization, HBsAg seroconversion, and histology improvement, compared NA's monotherapy [84]. In other studies, though higher on-treatment virological response was seen in patients on PEG-IFNα with lamivudine, sustained off-treatment virological or serological response was not any better compared to mono therapies [34,35]. However, it necessitates the need for long-term studies for analyzing the efficacy of combination therapies in future for the management of HBeAg positive CHB patients.

Future challenges: Another debatable topic in the management of CHB patients with NA's is with regards to partial virological responders. Partial virological response has been defined as > 1 log 10 IU/ml decrease in HBV DNA but detectable after at least 6 months of therapy in compliant patients [3]. Recommendations for this scenario, at week 24 in patients receiving lamivudine or telbivudine, or at week 48 in patients receiving adefovir; are to consider changing to either entecavir or tenofovir. However partial responder's to ETV and TDF at week 48, is managed by experts with the same agent in case of declining HBV DNA kinetics or by adding another agent in case of non-declining HBV DNA kinetics [3]. Recently, the results from a study in treatment naïve HBeAg (+) CHB patients on ETV monotherapy have raised concerns about the current guidelines criteria for defining primary non-response on ETV therapy. Primary virological non-response has been defined as <1 log decrease after 3 months by EASL or as <2 log drop after 6 months by AASLD. But, the study results have shown that the rate of primary non-response to be very low and no significant difference in the cumulative rate of virological response between primary responders and non-responders [85]. Several experts have suggested, to increase the on-treatment monitoring for ETV or TDF from the guidelines recommendation of every 3-6 months to 6 months once after patient compliance is confirmed.

Optimal management for HBeAg negative chronic hepatitis B patients

HBeAg-negative hepatitis B infection is currently the predominant type of CHB worldwide, especially in the western countries and is more difficult-to-cure with frequent progression to end-stage liver disease and HCC [3].

Approach to HBeAg negative patients for anti-viral therapy (Figure 3):

a) During the non-replicative or inactive HBV carrier phase: The most vital step in the management of these patients is their differentiation from chronic HBeAg negative CHB, which requires serial testing of ALT every 3 months and HBV DNA every 3-6 months for at least one year. Current guidelines suggest once you designate a patient as inactive HBV carrier by absence of HBeAg and presence of anti-HBe, undetectable or low levels of HBV DNA in PCR-based assays, repeatedly normal ALT levels, and minimal or no necroinflammation, slight fibrosis, or even normal histology on biopsy; treatment and liver biopsy can be deferred as their prognosis is usually benign [1,3]. Long-term follow-up of these carriers has indicated that the vast majority shows sustained biochemical remission and very low risk of cirrhosis or HCC [86]. Also, there isn't enough evidence to support any therapy that truly creates an impact on the HBsAg status. Precautions such as family screening, vaccination of the member's negative for HBsAg, protected sexual intercourse, avoidance of alcohol, denial of organ or blood donations and screening with alpha fetoprotein (AFP) and ultrasound (USG)

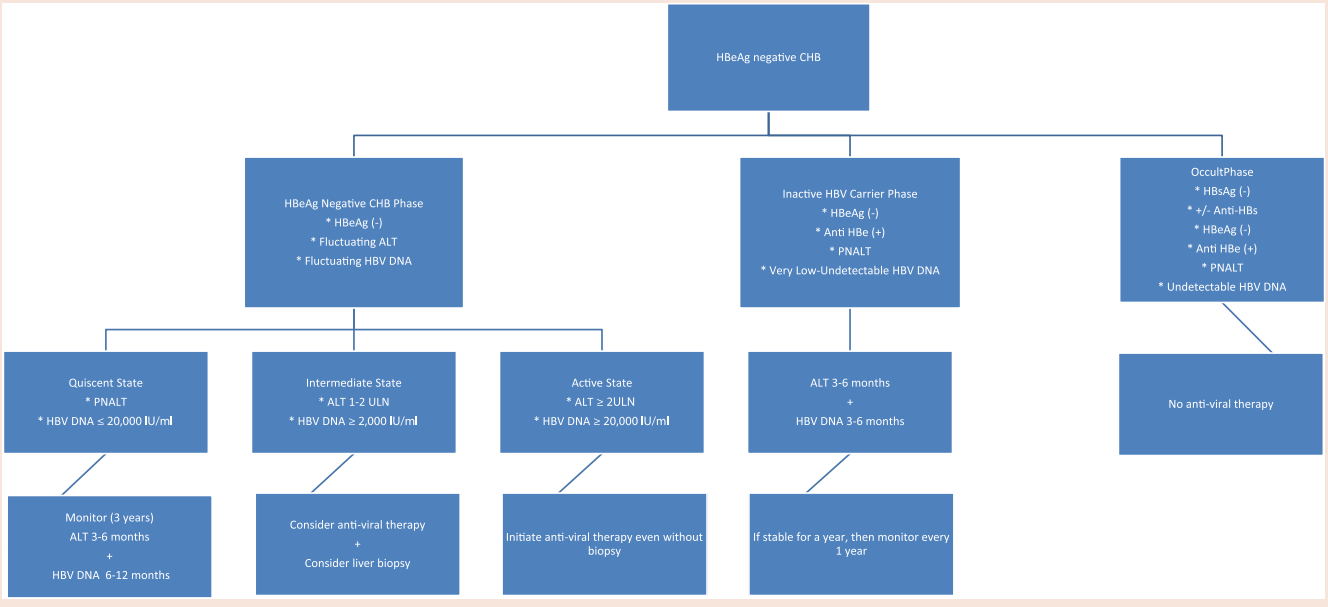

Figure 3: Approach to HBeAg Negative Chronic Hepatitis B patients.
CHB: Chronic hepatitis B; ALT: Alanine aminotransferase; PNALT: Persistently normal ALT; ULN: Upper limit of normal; HCC: Hepatocellular carcinoma; HBsAg: Hepatitis B surface antigen.

abdomen in case of positive family history of HCC should be undertaken regarding these patients [1,3].

b) During the HBeAg negative CHB phase: As mentioned earlier, these patients are characterized by periodic reactivation with a pattern of fluctuating levels of HBV DNA and aminotransferases and active hepatitis and continued necro-inflammation in the liver. The treatment strategy of these patients should also be individualized according to their clinical profile.**Active state:** AASLD & EASL clinical guidelines recommend to initiate treatment even without biopsy in all these patients, with persistent ALT > 2 ULN (upper limit of normal) and HBV DNA ≥ 20 000 IU/ml [1,3]. However, APASL guidelines differ little by having HBV DNA ≥ 2000 IU/ml as the cut-off to the similar picture [4]. A liver biopsy or fibroscan should be followed to rule out cirrhosis, although it has no say on the treatment strategy.

- **Intermediate state:** In patients with ALT 1-2 ULN and HBV DNA ≥ 2000 IU/ml, all guidelines recommend treatment consideration and liver biopsy. In patients with no to mild histological disease, treatment can be deferred [1,3,4].
- **Quiescent state:** Histologically significant liver disease is rare in HBeAg-negative patients with persistently normal ALT levels (PNALT) defined by 3 normal ALT readings 3 months apart and serum HBV DNA ≤ 20,000 IU/ml. Current guidelines recommend close follow-up without treatment in all these patients in the HBeAg negative CHB phase, without any evidence of liver disease [1,3]. The mandatory close follow-up involves ALT monitoring every 3 months and HBV DNA every 6-12 months for at least 3 years. After the follow-up period of 3 years, these patients can be managed like inactive chronic HBV carriers with fibroscan to evaluate the severity of fibrosis.

Cirrhotic state: Treatment is generally initiated in HBeAg negative CHB patients with compensated cirrhosis and HBV DNA ≥ 2000 IU/ml even if ALT levels are normal [1,3]. However, treatment should also be considered in patients with compensated cirrhosis with HBV DNA < 2000 IU/ml, if ALT is elevated. AASLD and EASL guidelines recommend urgent start of anti-virals in patients with decompensated cirrhosis and detectable HBV DNA [1,3]. Whereas, APASL recommend treatment in decompensated cirrhotic patients irrespective of HBV DNA levels [4].

Role of interferon's in HBeAg (-) CHB patient's management:

a) Standard vs. pegylated IFN: The usage of Standard IFNα for the HBeAg negative CHB patients has been substituted by PEG-IFNα because of the previously mentioned enhanced pharmacokinetic profile such as longer half-life, absence of wide fluctuations in serum concentrations, once a week subcutaneous injections, thereby improving compliance, reducing adverse events and enhancing viral suppression [1,3].

b) Endpoints for treatment: In HBeAg negative patients, though ultimate endpoint is sustained off-therapy HBsAg loss with or without anti-HBs, sustained off-therapy undetectable HBV DNA levels and ALT normalization are shown to be associated with improved prognosis [1,3].

c) Predictors of response to treatment: Since only a minority of HBeAg negative patients treated with PEG-IFNα achieved sustained virological response and for its side-effect profile, it is indispensable to identify the patients who are likely to benefit from treatment based on certain baseline parameters [87]. Earlier studies have showed enough evidence about high baseline ALT, low baseline HBV DNA, younger age and female gender being independent predictors of response to PEG-IFNα [88]. However the major challenge about these predictors is associated with the natural phase of chronic HBeAg negative infection, where the liver enzymes and viremia tends to fluctuate, making the already defined baseline predictors very unreliable. Recent interest is in the genetic testing for IL28B polymorphisms to prioritize CHB patients for IFN-based therapy. Some authors showed that in genotype D HBeAg-negative CHB patients; the IL28B rs12979860 genotype CC patients had better rates of SVR and HBsAg clearance than the non-CC patients [89]. However contradictory results were reported in other studies concluding polymorphisms near the IL28B gene were not associated with on- and post-treatment kinetics of HBV DNA and HBsAg levels, or with 24-week post-treatment responses [90].

HBsAg: On the other hand, with the availability of Architect HBsAg assay (Abbott Diagnostics, Abbott Park, IL, USA) and the Elecsys HBsAg II quant assay (Roche Diagnosticks, Indianapolis, IN, USA), there is increasing evidence on the role of baseline HBsAg and its kinetics during treatment as a predictor of a sustained response. Existing data suggests that baseline HBsAg level below 400 IU/ml is associated HBsAg loss with corresponding positive predictive value (PPV) of 100% and a negative predictive value (NPV) of 95% [91]. However, HBsAg variations according to the natural course of infection and HBV genotypes have proposed genotype-specific time frames and specific end-of-treatment thresholds to improve response-guided treatment of HBeAg-negative CHB [92,93]. The on-treatment decline in HBsAg > 0.5 log10 at week 12 and >1 log10 IU/ml at week 24 have shown a 89% and 92% chance of SVR, with corresponding 10% chance in patients who failed to achieve this decline [94,95]. Also, studies have stated patients with no decline of HBsAg levels and a decrease of HBV DNA of <2 log10 copies/ml at week 12 predicts non-response in genotype D HBeAg negative patients treated with PEG-IFNα [96]. The results of the stopping rule had a NPV of 100% and were confirmed by several other reports [97]. This application of early stopping rule optimizes the effectiveness of PEG-IFNα therapy by avoiding unnecessary treatment in patients with HBeAg-negative CHB (genotype D) who have no chance of achieving a sustained response.

d) Efficacy and durability of therapy: Initial cohort studies in HBeAg-negative CHB, which used 12 or 24-month courses of standard IFNα therapy have showed biochemical and virological responses in 22– 30% of patients with > 40 clearing HBsAg [98,99]. Subsequent studies with 48-week course of PEG-IFNα-2a have been reported to induce SVR off-therapy in approximately 36-43 % patients with rates of HBsAg clearance increasing from 3% at end of therapy to 9% and 12% after a follow-up of 3 and 5 years, respectively [100].

Recent data suggest that HBeAg negative genotype D patients could benefit from extending therapy beyond 48 weeks [101].

Randomized controlled study in 128 HBeAg negative CHB patients (94% genotype D) showed that patients treated with PEG-IFNα-2a for 96 weeks, compared to those treated with PEG-IFNα-2a for 48 weeks had better rates HBV DNA <2000 IU/ml (29% vs. 12%) and HBsAg clearance (5.8% vs. 0%) [102]. Also, the application of extended use PEG-IFNα in the management of HBeAg negative genotype D patients was supported by studies showing no significant difference in tolerance levels, adverse events and discontinuation rate between the two groups [102].

Role of NA's in the management of HBeAg negative CHB patients:

a) Early vs. late NA's: Among the NA's, entecavir (ETV) or tenofovir (TDF), are the first-line drugs recommended for treatment-naïve HBeAg negative chronic hepatitis B patients. These agents are not only potent than other existing NA's, but also has high barrier to resistance.

Studies have reported the cumulative probability of developing resistance to lamivudine increased over the period of time in HBeAg negative patients, from 10% after 1 year of therapy to as high as 63% after 5 years of therapy [103]. Also, it resulted in a progressively lower rate of undetectable HBV from 73% at 1 year to 34% at 4 years and ALT normalization from 84% to 36% [104]. A phase III clinical trial including HBeAg negative CHB patients, reported significantly higher rates of histologic responses (70% vs. 61%), undetectable HBV DNA levels (90% vs. 72%) and ALT normalizations (78% vs. 71%) in subjects on ETV compared to 3TC [105]. Another study reported that the relapse rate was very high (>90%) after 1 year of stoppage of 3TC [106]. Studies analyzing the cumulative probability of developing resistance to adefovir have shown a similar picture to lamivudine, with increasing resistance over the period of time in HBeAg negative patients, from 0% after 1 year of therapy to 11% and 29% after 3 and 5 years of therapy, respectively [107]. In a phase III clinical trial, patients on TDF reported significantly higher rates of undetectable HBV DNA levels (93% vs. 63%) compared to patients on adefovir [108]. Also, switching to tenofovir resulted in further virus suppression in the patients originally treated with adefovir. Though telbivudine response rates have better than 3TC in the phase III clinical trials, genotypic resistance after 1 and 2 years of treatment was still observed in 2.3% and 10.8% of HBeAg-negative patients who received telbivudine [109]. The earlier NA's 3TC and adefovir had another drawback of holding the durability of response as studies have reported the rate to be < 10% in HBeAg (-) individuals [110,111].

b) Endpoints for treatment: Since HBV eradication or clearance of HBsAg is almost impossible with NA's; a more realistic aim is the normalization of ALT activity, persistent inhibition or at least significant suppression of HBV replication and prevention of cirrhosis and HCC.

c) Predictors of response to treatment: In contrast to HBeAg positive CHB treatment, evidences showing the baseline predictors of response to NA's in the management of patients with HBeAg (-) CHB are not widely available [112]. At the same time, HBV genotype does not influence the virological response to any NA. However, these agents are preferred over PEG-IFN in patients with more severe liver disease, in older patients, and those who do not respond, unwilling to take or have contraindications to PEG-IFNα.

d) Efficacy and durability of therapy: The efficacy of ETV and TDF has been very remarkable in the management of treatment naïve HBeAg negative CHB patients. European field practice studies including 1162 CHB patients treated with ETV have reported the cumulative probability of achieving a virological response at year 5 as 97% and 99% [113]. Similar efficacy reports were seen in Asian studies, where 98% and 95% of patients on ETV achieved undetectable HBV DNA at year 5 [114-116]. The rate of ETV resistance was also very low (<1%), that were managed with substitution to TDF. TDF-registration trials have reported that the rates of undetectable HBV DNA ranges from 92 to 100% from 3 to 7 year course of TDF therapy, with no resistance reported in any of their patients [117].

Partial virological response to ETV or TDF is very rare. Studies have shown that it acceptable to treat with same drug if the residual viremia is ≤1000 IU/ml and to consider a switch strategy of substituting TDF for partial response to ETV and vice versa, only if residual viremia is >1000 IU/ml or a flat pattern in serum HBV DNA levels is seen [118]. Despite its efficacy, the rates of HBsAg loss following 12 months of ETV or TDF are close to zero [119,120]. Long-term effective ETV and TDF treatment have been shown to induce regression of fibrosis in two-thirds of patients with cirrhosis, especially in all compensated patients, thereby preventing clinical decompensation [121,122]. Also, in patients with decompensated liver disease, survival was significantly improved because of persistent HBV DNA suppression. In Asian and European studies, the annual incidence of HCC in patients with cirrhosis receiving ETV and TDF was reported to range from 2-4% and 3.7-4% respectively, and in patients without cirrhosis it ranged from 0.6-1.4% and 0.4-1% respectively [123,124]. Long-term administration of ETV or TDF was also associated with low rates of severe AEs and drug discontinuation. [125].

Selection between NA's and PEG-INF in HBeAg negative patient's treatment (Figure 4): TDF and ETV are the only treatment options for patients with severe liver disease, elderly patients, or those with contraindications to or unwilling to take PEG-IFNα as well as those with certain severe associated diseases. However, long-term administration of ETV or TDF cannot eradicate HBV making long-term therapy necessary in most patients, increasing the cost, creating compliance issues and unproven safety profiles. The finite course of PEG-IFN is still an impressive strategy in patients who are young with high ALT levels and low HBV DNA and appropriate virus genotype.

a) Combination therapies: Combination therapies are starting to become the future possible options in the management of HBeAg negative CHB patients. Earlier studies involving PEG-IFN with 3TC or adefovir have shown a higher on-treatment virological response rate but no benefit in of treatment SVR or serological response [126]. In PARC trail, the addition of ribavirin did not improve the efficacy of a 48-week course with PEG-IFNα offering similar rates of combined responses at 6 months [127]. A promising approach to improve HBsAg clearance rates could be the add-on or switch to PEG-IFNα therapy among the responders to NA's [128]. There have been promising results in small studies evaluating this approach

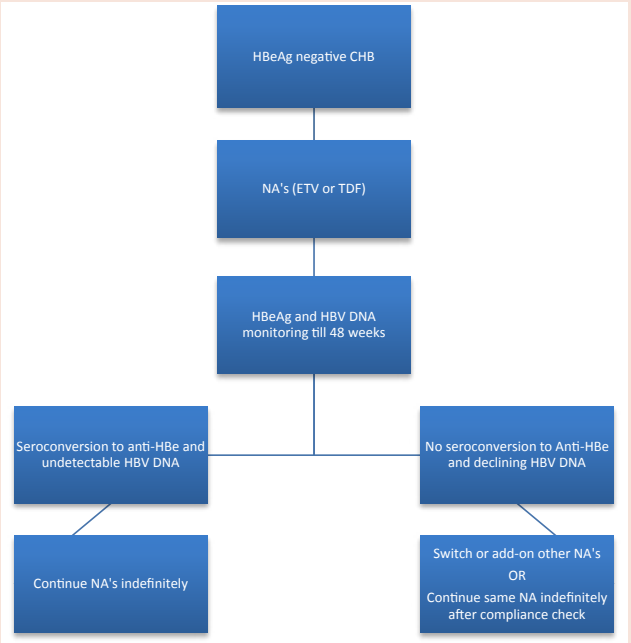

Figure 4: Anti-viral Therapy Options for HBeAg Positive Chronic Hepatitis B patients.
CHB: Chronic hepatitis B; NA's: Nucleos(t)ide analogues; ETV: Entecavir; TDF: Tenofovir; ALT: Alanine aminotransferase.

[129]. In one study adefovir was given for 20 weeks and was followed by adefovir and PEG-IFNα for 4 weeks and finally PEG-IFNα alone for 44 weeks. Twenty-four weeks after the end of PEG-IFNα, 50% had either partial (HBV DNA <10 000 copies/ml) or complete (HBV DNA <70 copies/ml) virological response [130]. In another study, the SVR (HBV DNA <2000 IU/ml) was significantly higher in patients treated with telbivudine first followed by PEG-IFNα than vice versa (46.7% vs. 13.3%, P = 0.046) [131]. Following a slightly different concept, few patients with PEG-IFNα added to a stable and effective NA therapy, showed a rapid decline in HBsAg resulting in anti-HBs development at weeks 32 or 40 [132]. These preliminary results suggest that the combined use of NAs and PEG-IFNα may be effective, but need further studies to reveal their potential benefits and determine whether they are worth pursuing.

Conclusion

Currently, the existing therapeutic strategies for the management of patients with chronic hepatitis B infections are the pegylated IFNα and nucleos(t)ide analogues. Among these, entecavir (ETV) and tenofovir (TDF) are most the favored treatment options in both HBeAg positive and HBeAg negative patients, as they can be used in all chronic HBV patients and are more convenient to use for its oral administration, excellent tolerance, good safety profile and minimal or no risk of long-term resistance. Despite their virological, biochemical and histological benefits in nearly all-adherent patients, HBV eradication is not possible and hence the risk of HCC, resulting in long or indefinite periods of therapy. In the future, novel therapeutic targets or creative combination therapies of adding a finite course of PEG-IFNα to NA's might be desirable to increase the sustained virological response rates, achieve HBV eradication or at least substantially increase the rates of HBsAg loss and seroconversion.

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